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(54) Title: RESOLUTION OF RITALINIC ACID SALT

(57) Abstract

A process for preparing an enantiomerically–enriched form of *threo*–retalinic acid, which comprises resolving a mixture of enantiomers of a salt of the acid, said salt being formed with an achiral acid or base, using a chiral resolving agent. The resolved salt can be esterified, to give the therapeutic agent *d–thero*–mehylphenidate.

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RESOLUTION OF RITALINIC ACID SALT

Field of the Invention

This invention relates to an economic process for the manufacture of a single isomer of a precursor to *d-threo*-methylphenidate.

Background to the Invention

Methylphenidate is a therapeutic agent that is widely used in the treatment of attention-deficient hyperactivity disorder. It is a controlled substance.

Methylphenidate was first prepared as a mixture of the *erythro* [*R*S**] and *threo* [*R*R**] racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereoisomer. It is now considered that it is the d-*threo* [or (*R,R*)] enantiomer that has the preferred therapeutic activity. Uses of this enantiomer are disclosed in WO-A-9703671, WO-A-9703672 and WO-A-9703673, the contents of which are incorporated herein by reference.

The resolution of *threo* methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, a process first reported by Patrick *et al*, The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987). More efficient resolutions, using a *O,O'*-diaroyltartaric acid or menthoxyacetic acid, are disclosed in WO-A-9727176 and in PCT/GB97/00643, the contents of which are incorporated by reference; in particular, the use of *O,O'*-di-*p*-toluoyltartaric acid allows the diastereoisomeric salts to be very readily separated, to give the desired enantiomer in high enantiomeric excess and high chemical purity.

In an alternative approach, disclosed in US-A-2957880, the amide of *erythro* methylphenidate (i.e. as $-CONH_2$ instead of $-CO_2Me$) is resolved using tartaric acid. However, this resolution must be followed by amide hydrolysis, and equilibration at the benzylic centre, to give the *threo* isomer of the carboxylic acid which is esterified.

It would be desirable to find a satisfactory substrate for resolution that did not involve handling the active drug. Ritalinic acid might be a target, and is a common intermediate, in *threo* form, in synthesis preceding or following the two respective resolutions described above.

US-A-2957880 discloses single isomer ritalinic acid hydrochloride. It is prepared (see Example 6) from the corresponding acid amide.

Summary of the Invention

The present invention is based on the surprising discovery that, although ritalinic acid will not undergo any effective degree of resolution with any of a wide range of resolving agents, a salt thereof is an effective substrate for resolution, e.g. with a chiral base. In a particular preferred embodiment of the invention, *threo*-ritalinic acid hydrochloride is resolved with (-)-1-phenylethylamine. The chiral base may form a novel double salt.

Description of the Invention

For the purposes of illustration at least, the salt that is the substrate for resolution according to this invention may be prepared by base hydrolysis of methylphenidate, using NaOH or another hydroxide (MOH). A suitable acid salt may then be prepared by adding an acid (HX) that releases M from the resultant salt (e.g. a metal or ammonium salt) of ritalinic acid. On passing the isoelectric point, it appears that the piperidine N atom is protonated. Alternatively, preparation of salts may be *via* acid hydrolysis of methylphenidate.

The resolution is conducted using conditions that are generally known in the art. Examples of suitable chiral bases are 1-phenylethylamine, and also 1-(1-naphthyl)ethylamine, cinchonine, cinchonidine and N-methyl-D-glucamine. The use of, say, (-)-1-phenylethylamine gives the preferred d-*threo*-enantiomer of ritalinic acid salt. That can be converted to d-*threo*-methylphenidate hydrochloride by reaction with methanol and HCl, with heating.

Salts that are substrates for resolution according to this invention have good or at least adequate solubility in various solvents, especially polar solvents, including aqueous systems. Adjustment of pH, e.g. by adding acid (which may be ritalinic acid), can enhance solubility.

The following Example illustrates the invention.

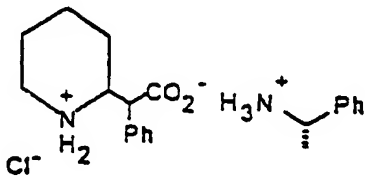
Example

A solution of dl-*threo*-methylphenidate (1 g) in water (25 ml) and conc. HCl (5 ml) was heated under reflux for 3 h. The clear solution was evaporated to dryness, to give a dl-*threo*-ritalinic acid hydrochloride as a white solid.

Resolution was performed using this salt. The salt (175 mg; 0.8 mmol) was placed in a 10 ml round-bottom flask. Ethanol (5 ml) was added, to give a clear solution. (-)-1-

Phenylethylamine (0.1 ml; 0.8 mmol) was added. A gelatinous precipitate formed after a few minutes. Water (15 drops) was added, and the mixture stirred for 2 h. White crystals formed within 1 h. Following stirring overnight, crystals (40 mg) were collected on a sinter. Chiral HPLC analysis showed the crystals to comprise a diastereoisomeric salt enriched in *d-threo*-ritalinic acid, of 77% ee, and the mother liquors containing the opposite diastereoisomer enriched in *l-threo*-ritalinic acid, of at least 23% ee.

A crystalline ritalinate salt is formed when ritalinic acid hydrochloride is mixed with 1-phenylethylamine but does not form when the ritalinic free amino-acid is mixed with 1-phenylethylamine. NMR shows that this salt contains ritalinate and is thus not simply 1-phenylethylamine hydrochloride. From these observations, it is deduced that the salt is the double salt depicted below. The salt is also a hydrate, since only a gelatinous precipitate is formed in anhydrous ethanol, whereas in 95% ethanol/5% water white crystals are formed.



CLAIMS

1. A process for preparing an enantiomerically-enriched form of *threo*-ritalinic acid, which comprises resolving a mixture of enantiomers of a salt of the acid, said salt being formed with an achiral acid or base, using a chiral resolving agent.

2. A process according to claim 1, wherein said salt is formed with an achiral amine or acid.

3. A process according to claim 2, wherein said salt is formed with an acid of the formula HX, X being any anion.

4. A process according to claim 3, wherein said salt is the hydrochloride.

5. A process according to any preceding claim, wherein the enrichment is at least 70%.

6. A process according to any preceding claim, wherein the resolving agent is an amine.

7. A process according to claim 6, wherein the amine is (-)-1-phenylethylamine.

8. A process according to any preceding claim, wherein the d-enantiomer is enantiomerically-enriched.

9. A process for preparing *d-threo*-methylphenidate, which comprises conducting a process according to claim 8 and then subjecting the product to reaction with methanol or esterification with a methylating agent.

10. A double salt of *threo*-ritalinic acid, predominantly as a single enantiomer thereof, wherein one counterion is achiral and the other is derived from a chiral resolving agent.

11. A double salt according to claim 10, wherein the achiral acid or base is as defined in any of claims 2 to 4.

12. A double salt according to claim 10 or claim 11, wherein the chiral resolving agent is as defined in claim 6 or claim 7.

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/GB 98/00112

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2 957 880 A (R. ROMETSCH) 25 October 1960 cited in the application see the whole document ---	1-12
A	CHEMICAL ABSTRACTS, vol. 83, no. 13, 29 September 1975 Columbus, Ohio, US; abstract no. 114219, YAKHONTOV L.N. ET AL.: "Methyl threo-alpha-phenyl-alpha-(2-piperidyl)acetate hydrochloride" XP002049166 see abstract & SU 466 229 A (ALL-UNION) --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 107, no. 3, 20 July 1987 Columbus, Ohio, US; abstract no. 17704, PATRICK, KENNERLY S. ET AL.: "Pharmacology of the enantiomers of threo-methyl-phenidate" XP002049169 see abstract & J. PHARMACOL. EXP. THER., vol. 241, no. 1, 1987, pages 152-158, cited in the application	1-12
A	E.J. COREY ET AL.: "A new stereocontrolled synthesis of prostaglandins via prostaglandin A2." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 95, no. 20, 3 October 1973, DC US, pages 6832-6833, XP002049164 see page 6832, paragraph 2 - page 6833; figure 2	1-12
P,A	WO 97 28124 A (MEDEVA EUROPE LIMITED) 7 August 1997 see the whole document	1-12
P,A	WO 97 32851 A (MEDEVA EUROPE LIMITED) 12 September 1997 see the whole document	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/GB 98/00112

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WO 9728124 A	07-08-97	AU 1608297 A	22-08-97
WO 9732851 A	12-09-97	AU 2102497 A	22-09-97